High yield of synchronous lesions in referred patients with large lateral spreading colorectal tumors

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Abstract

Background and Aims

There are few data on the prevalence of synchronous colorectal lesions in patients who have large lateral spreading tumors. We sought to describe the rate of synchronous lesions found in patients who underwent endoscopic resection of large sessile adenomas and serrated lesions.

Methods

This is a retrospective assessment of a prospectively created database of 728 consecutive patients with large lateral spreading tumors (LLST) resected who underwent complete clearing of the colon during two colonoscopies by a single expert endoscopist.

Results

The 728 patients with resected LLSTs and complete clearing had 4578 synchronous lesions, including 584 patients (802%) with at least one synchronous conventional adenoma, 132 (18.1%) with at least one synchronous conventional adenoma ≥ 20 mm in size, 294 (40.4%) with at least one synchronous advanced conventional adenoma, and 6 patients with a synchronous lesion with cancer. Patients with an index large sessile conventional adenoma compared to those with an index large serrated lesion had on average more synchronous conventional adenomas (4.8 vs 2.9, $p=0.001$) and fewer synchronous serrated lesions (1.4 vs 4.5, $p<0.001$). Of the 97 patients with a serrated class index lesion, 28 (28.9%) met criteria for serrated polyposis.

Conclusions

There is a very high prevalence of synchronous lesions, including other large and advanced synchronous lesions, in patients with flat or sessile conventional adenomas and serrated

colorectal polyps. Patients with large lateral spreading tumors in the colon need detailed clearing of the rest of the colon. Patients referred for endoscopic resection of serrated lesions ≥ 20 mm have a very high prevalence of serrated polyposis. This study has potential implications for further stratification of high risk patient groups in post-polypectomy surveillance guidelines.

Introduction

Guidelines emphasize high quality colonoscopy examinations to decrease the risk of interval cancer.[1] Large colon polyps are associated with an increased risk of developing metachronous advanced neoplasia at the interval exam.[2] However, this may be attributable to missed synchronous lesions as opposed to early metachronous lesions. Prior studies demonstrated an increased risk of synchronous advanced adenomas in patients with large flat polyps[3], large sessile adenomas[4] and large serrated polyps[5-11].

The aim of this study is to systematically describe synchronous lesions found in patients who underwent endoscopic resection of large (≥ 20 mm in size) lateral spreading tumors. To our knowledge, this is the largest study to address this issue.

Methods

This is a retrospective evaluation of a prospectively created database of large (≥ 20 mm in size) lateral spreading tumors (LLST) referred to and resected by a single endoscopist (DKR) between April 2000 and December 2015. Review of the database was approved by the Institutional Review Board at Indiana University Health Partners on June 16, 2015.

In many cases DKR removed the LLST during the baseline colonoscopy but did not clear the entire colon until the first follow-up colonoscopy. Patients were encouraged to return to our center within 3-6 months for surveillance of the polypectomy site with clearance of the remaining colon, but some patients underwent follow-up colonoscopy by the referring physician because of travel distance. Patients were included if they had at least 2 colonoscopies performed

by DKR within 1 year. Patients were excluded if they had known familial adenomatous polyposis, if the index large polyp was pedunculated, < 2 cm in maximum diameter, or if it was not an adenoma, serrated lesion, or cancer (e.g. inflammatory polyp). Synchronous inflammatory polyps and other non-adenomatous/non-serrated class lesions are not reported here.

The database contains patient demographics, polyp information, and histopathologic data. The largest lesion in a patient was considered the index LLST. Polyps were considered synchronous if they were identified during the baseline procedure or any subsequent procedure within 12 months. There were 658 cases in which the LLST was referred by another colonoscopist and 70 cases in which the study endoscopist detected the index LLST during a screening, surveillance, or diagnostic colonoscopy. The colonoscopy and pathology reports from the referring physician and institution were available in all cases at the time of the initial LLST resection at our center but were entered into our database in only 328 of the 658 cases. To try and capture the full degree of synchronous lesions, synchronous polyps resected by the referring endoscopist were included if the procedure and pathology reports were available in our database.

Conventional adenomas included tubular adenomas (TA), tubulovillous adenomas (TVA), or villous adenomas (VA). Serrated lesions included sessile serrated polyps/adenomas (SSP), hyperplastic polyps (HP), and traditional serrated adenomas. Advanced synchronous conventional adenomas were defined as lesions ≥ 10 mm in size, or lesions with high grade dysplasia, cancer, or villous elements. Advanced synchronous serrated lesions included SSP ≥ 10 mm and SSP with cytological dysplasia. HP ≥ 10 mm in size were recorded separately. Serrated polyposis syndrome (SPS) was defined based on World Health Organization criteria: 1) ≥ 5

serrated class polyps (SSP or HP) proximal to the sigmoid colon with 2 or more ≥ 10 mm; 2) any number of serrated class polyps proximal to the sigmoid colon in a patient with a first-degree relative with SPS; 3) ≥ 20 serrated class polyps distributed throughout the colon.[12]

Statistical analysis was performed using SPSS version 23 (IBM, New York, NY). Means and standard deviations were calculated for continuous variables. Means between groups were compared using either the Student's t-test for normal distribution or the Wilcoxon rank sum test.

Results

There were 1029 consecutive patients with sessile or flat lesions ≥ 20 mm in diameter that were identified in the database. 296 patients were excluded because they only had 1 colonoscopy performed by DKR. Patients had only one colonoscopy if they did not return to our center for follow-up (n = 239), if they were referred for surgical resection because the index lesion had endoscopic features of cancer (these lesions were biopsied and referred to surgery, n = 24), or if they were considered endoscopically unresectable (n = 33). Three patients were excluded for known familial adenomatous polyposis at the time of referral. Two were excluded because the index LLST was an inflammatory polyp. 728 patients with an LLST resected and who underwent two colonoscopies by DKR were included in this study.

Of the 728 patients, the mean age was 65.8 ± 10.5 years (range 24-90 y) and 349 (47.9%) were female. The mean interval between the two colonoscopies was 144 days (range 12-365 days). The largest LLST for which the patient was referred for endoscopic resection was considered the index lesion, and all additional lesions were considered synchronous. The index lesion was

determined by the referring doctor's colonoscopy report and in most cases was tattooed by the referring physician. The 728 index LLSTs are described in Table 1 by histology and location. The size of the LLST ranged from 20-29 mm (n=292), 30-39 mm (n=255), 40-49 mm (n=87), 50-59 mm (n=67), and greater than 60 mm (n=27).

A total of 4578 synchronous lesions were resected, which are described in Table 2 by histology, size, and location. 584 patients (80.2%) had at least one synchronous conventional adenoma, 132 (18.1%) had at least one synchronous conventional adenoma ≥ 20 mm in size, 294 (40.4%) had at least one synchronous advanced conventional adenoma, and 6 patients had a synchronous lesion with cancer. 2174 (47.5%) of the synchronous polyps were located in the same colon segment or in an adjacent segment to the LLST, and 2404 (52.5%) of the synchronous polyps were located more than one segment away from the LLST.

In 594 patients with only 1 LLST, there were 3266 synchronous lesions resected, including 2323 synchronous conventional adenomas, 336 synchronous advanced conventional adenomas, 125 synchronous SSP, and 38 synchronous HP ≥ 10 mm. 459 (77.3%) had at least one synchronous conventional adenoma, 162 (27.3%) had at least one synchronous advanced conventional adenoma, and 6 patients had a synchronous lesion with cancer.

Table 3 compares the number of synchronous lesions per patient between different groups of patients. Those patients for whom their colonoscopy and pathology report from the referring institution were in our database had more synchronous adenomas (5.5 vs 3.7; $p<0.001$) and more synchronous serrated class lesions (2.7 vs 0.9; $p<0.001$). Patients with an adenomatous index

LLST compared to those with a serrated index LLST had more synchronous conventional adenomas (4.8 vs 2.9, p=0.001) and fewer synchronous serrated class lesions (1.4 vs 4.5, p<0.001). Patients with more than 1 LLST had more synchronous lesions (9.9 vs 5.5, p<0.001). Male patients had more synchronous adenomas (5.3 vs 3.6, p<0.001).

There were 37 patients who had newly diagnosed serrated polyposis syndrome, and they had significantly more serrated lesions compared with the other patients (10.0 vs 1.4, p<0.001). The criteria for SPS in the 37 patients included 33 with WHO criteria 1, one with WHO criteria 2, and three with WHO criteria 3. Of the 97 patients with a serrated index LLST, 28 (28.9%) met criteria for SPS.

There were 13 patients (1.8%) identified with cancer in this population, including 7 with cancer in the resected index lesion and 6 (0.8%) with cancer in a synchronous lesion. In these patients, the size of the synchronous cancers averaged 14.7 mm (range 10-20 mm), and the size of the index LLST cancers averaged 33 mm (range 20-65 mm). All of the 6 synchronous cancers occurred in referred patients and were depressed lesions with residual conventional adenoma (Figure 1).

Discussion

In this report we describe the prevalence of synchronous lesions in 728 primarily referred patients with large flat or sessile colorectal lateral spreading tumors who underwent colonoscopic clearance over two colonoscopies by a single expert endoscopist. The prevalence of synchronous conventional adenomas and synchronous serrated class lesions was very high. Our study

indicates that patients with large sessile or flat lateral spreading tumors ≥ 20 mm in size demand detailed clearance of the colon for synchronous lesions. Patient should also have lesions counted to see if they meet the criteria for serrated polyposis, as 28.9% of patients with an index serrated lesion greater than 20 mm in size met the criteria for serrated polyposis.

Prior studies demonstrated a high rate of advanced synchronous conventional adenomas (27%-44%) in patients with serrated class polyps ≥ 10 mm.[5-9,11] We also found a high rate of synchronous conventional adenomas in patients with large serrated polyps ≥ 20 mm, but we also demonstrated a high risk of synchronous serrated class lesions in this population. Only two prior studies characterized synchronous lesions in patients with conventional adenomas ≥ 20 mm.[3,4] The larger study[4] included 582 patients who underwent EMR of large flat colon polyps ≥ 20 mm with a complete colonoscopy. Relevant findings of that study included 67% of patients with synchronous polyps, 52% with synchronous adenomas with low grade dysplasia, 8% with synchronous adenomas with high grade dysplasia, and 17% with synchronous serrated class lesions. Our findings demonstrate an even higher prevalence of synchronous lesions in a primarily referred patient population. The demonstration of patients with synchronous cancers is also concerning and emphasizes the need for detailed clearing of the colon. In this report 6 of 658 referred patients (0.9%) had a synchronous cancer in the colon that had escaped detection by the referring physician. In this study all of the synchronous cancers were flat depressions lesions, and this shape likely contributed to their escaping detection by the referring physician.

We found that synchronous lesions were common both within the same segment as the LLST and in segments distant from the LLST. Thus, our data indicate the need to clear the entire colon

carefully in patients with LLSTs. Interval cancers (post colonoscopy cancers) have been estimated to result largely from missed lesions but a minority of interval cancers are usually attributed to incomplete polypectomy.[13,14] The basis for implicating incomplete polypectomy in specific interval cancer cases is usually that the interval cancer arose in the same colonic segment where a polypectomy had been performed.[13,14] The high prevalence of synchronous pre-cancerous lesions in the same segment as the LLST suggests that in some cases interval cancers attributed to incomplete polypectomy were rather the result of missed synchronous lesions.

Our data suggest that large numbers of synchronous lesions in patients referred to our center were missed by referring colonoscopists. However, we speculate that the referring endoscopist sometimes stops looking for additional lesions once a need for referral is determined. This may be especially true for lesions in the same segment as the LLST, since the referring physician might reasonably consider that if we could not resect the LLST endoscopically at our center, that subsequent segmental surgical resection to remove the LLST would also remove synchronous lesions in the same segment. Alternatively, the bowel preparation at the initial examination performed by the referring physician might have interfered with detection of lesions, as poor bowel preparation is known to be followed by detection of a high yield of pre-cancerous polyps at follow-up examinations.[15] The precise reasons for the referring doctor leaving large numbers of synchronous lesions in the colon remain uncertain, so that we are unwilling to suggest that most lesions were missed by the referring colonoscopy. Rather, our data from the referring physician's records plus our finding establishes a remarkably high prevalence of synchronous neoplasia in patients with large LLSTs that demands careful and detailed complete colonoscopic clearance of the colon in patients with LLSTs.

Strengths of our study include its large size. This is the single largest cohort of lesions ≥ 20 mm in size resected by a single endoscopist or at a single center in the medical literature, and the largest study to address LLST and their synchronous polyps that includes the results of both a baseline and a second follow-up examination within one year. A second strength of the study is that the endoscopist has a proven high detection rate for both conventional adenomas[16,17] and serrated lesions[16,18]. This high detection rate should maximize the prevalence of synchronous lesions determined in the study. In addition, many patients in this report had other polyps resected by the referring endoscopist prior to referral of the index LLST to our center and the outside reports were available in only 49.8% (328 of 658) of the referred patients. Thus, the very high prevalence of synchronous lesions reported here underestimates the true prevalence of synchronous lesions in this population. Third, our study reports rates of synchronous lesions in patients with both large conventional adenomatous LLSTs and large serrated LLSTs. We have demonstrated that patients with large conventional adenomatous LLSTs have more synchronous conventional adenomas than serrated class lesions, and conversely patients with large serrated LLSTs have more synchronous serrated class lesions than conventional adenomas. Finally, the database used to determine rates of synchronous lesions in this study was created prospectively, though the current analysis was performed retrospectively.

The main limitation in this study is the likelihood of referral bias. Thus, the average size of the index LLST likely exceeds that of LLSTs that would be encountered by colonoscopists during routine colonoscopy. Further, in some instances, the referring physician may have been aware that multiple other lesions were present in addition to the index lesion, and referred the patient

partly because of the multiplicity of lesions rather than the difficulty of resecting the index lesion alone. However, we also found a high rate of synchronous lesions in the smaller number of study subjects (n=70; Table 3) whose index lesion was detected by the study endoscopist. Thus, despite the potential for referral bias, our results emphasize the need for colonoscopists to understand that patients with LLSTs can have extensive synchronous disease and require detailed clearing of the entire colon.

This report has potential implications for post polypectomy surveillance guidelines. The US Multi-Society Task Force recommended that patients with large sessile and flat lesions removed in piecemeal fashion should have a follow-up endoscopy to examine the site in 3 to 6 months.[1,19] Our own practice is to perform two follow-ups, one in the first 3 to 6 months, and the second approximately one year later.[4,20] The Australian experience on follow-up of large lesions removed by EMR, which is the largest consortium experience of EMR of large colorectal lesions reported, utilizes a very similar protocol.[21] Our data indicate that in addition to inspection of the index lesion resection site for recurrence, patients with LLST should also have a detailed inspection of the entire colon during these follow-up examinations. Our data also confirm a general tendency towards a high prevalence of synchronous lesions in patients with larger colorectal polyps.[4] Compared to the US recommendations for post polypectomy surveillance, guidelines in the UK have a broader range of surveillance interval stratification between the highest and lowest risk patients.[22] In the UK guidelines, patients with 3 or more adenomas, of which one is ≥ 10 mm in size, should have a follow-up examination in one year. US guidelines recommend that patients who have >10 adenomas should undergo colonoscopy in less than 3 years, with no reference to lesion size. The findings of a very high rate of synchronous lesions in

our study would tend to support a movement toward greater surveillance interval stratification in US recommendations at the high risk end of the risk spectrum, including shorter term follow-up and careful clearing for patients with multiple lesions that includes a large lesion.

In conclusion, there is a very high prevalence of synchronous lesions, including advanced synchronous lesions, in patients with large lateral spreading tumors. Patients with such lesions need detailed clearing of the remainder of the colon. Patients referred for endoscopic resection of serrated lesions ≥ 20 mm have a high prevalence of serrated polyposis.

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Table 1. Location and histology of index large lateral spreading tumors in 728 patients

	Tubular adenoma	Tubulovillous adenoma	Villous adenoma	Sessile serrated polyps	Hyperplastic polyps	Cancer
Rectum	19	49	7	1	0	2
Sigmoid	15	17	3	2	2	2
Descending	12	7	1	4	3	1
Splenic flexure	3	6	1	0	0	0
Transverse	69	24	0	10	2	1
Hepatic flexure	9	16	1	9	1	1
Ascending	91	92	5	42	4	0
Ileocecal valve	16	25	1	3	1	0
Cecum	58	75	2	11	2	0

Table 2. Location, histology, and size of 4578 resected synchronous lesions

	Tubular adenoma		Tubulovillous adenoma		Villous adenoma		Sessile serrated polyps		Hyperplastic polyps		Cancer
	<1 cm	≥1 cm	<1 cm	≥1 cm	<1 cm	≥1 cm	< 1 cm	≥ 1 cm	< 1 cm	≥ 1 cm	
Rectum	80	12	5	4	0	1	4	1	206	5	1
Sigmoid	325	44	18	21	0	3	29	7	334	16	2
Descending	256	38	3	7	0	2	10	3	65	9	1
Splenic flexure	19	3	0	0	0	0	0	0	3	0	0
Transverse	744	86	19	12	2	0	35	22	135	17	1
Hepatic flexure	86	17	2	3	0	0	7	7	31	6	0
Ascending	768	143	49	33	2	5	50	39	109	26	0
Ileocecal valve	16	10	1	2	0	1	0	0	7	0	0
Cecum	349	53	22	14	0	0	10	13	78	8	1

Table 3. Number of synchronous lesions per patient compared between different patient groups.

		Synchronous lesions per patient	p	Synchronous adenomas per patient	p	Synchronous serrated lesions per patient	p
Index lesion	Adenoma (n=624)	6.2	0.06	4.8	0.001	1.4	<0.001
	Serrated lesion (n=97)	7.4		2.9		4.5	
Index lesion, excluding SPS	Adenoma (n=616)	6.0	0.16	4.8	<0.001	1.2	<0.001
	Serrated lesion (n=69)	5.0		2.4		2.6	
# LLST	1 (n=596)	5.5	<0.001	3.9	<0.001	1.6	0.001
	>1 (n=132)	9.9		7.3		2.6	
Gender	Male (n=380)	7.1	<0.001	5.3	<0.001	1.8	0.68
	Female (n=348)	5.5		3.6		1.9	
Serrated polyposis syndrome	Yes (n=37)	14.7	<0.001	4.6	0.92	10.1	<0.001
	No (n=691)	5.9		4.5		1.4	
Referral	Referred (n=658)	6.5	0.02	4.6	0.10	1.9	0.07
	Not referred (n=70)	4.7		3.5		1.2	
Outside report of 660 referred	Available (n=328)	8.2	<0.001	5.5	<0.001	2.7	<0.001
	Not available (n=330)	4.8		3.7		1.1	

Figure 1. Four of the six synchronous cancers identified during the study. All 6 were relatively flat lesions with depressed centers